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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,899	09/28/2001	Markku Koulu	2630-111	5535

6449 7590 01/15/2004

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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,899	KOULU ET AL.	
	Examiner	Art Unit	
	Robert M Kelly	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-11* is/are pending in the application.

4a) Of the above claim(s) *4-7 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 4-11 are pending.

Claims 8-10 are considered in this action.

Claims 1-3 and 12-13 stand cancelled.

Election/Restrictions

Applicant's election without traverse of Group V, Claims 8-10 in Applicant's Response to Restriction, received *04 November 2003*, is acknowledged.

Applicant's election of Group V, Claims 8-10 in Applicant's Response to Restriction, received *04 November 2003*, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 4-7 and 11 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Applicant's Response to Restriction Requirement, received 4 November 2003.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Finland on 29 March 2000. It is noted, however, that applicant has not filed a certified copy of the PCT application as required by 35 U.S.C. 119(b).

Specification

The disclosure is objected to because of the following informalities: page 16 and page 17 contain subject matter which are considered drawings and not proper material for the specification.

Applicant is required to amend the specification and, if considered relevant, file these pages as drawings, and amend the specification to incorporate the figures without adding any new matter.

Appropriate correction is required.

If Applicant chooses to submit the aforementioned drawings, Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings.

Claim Objections

Claims 8-10 are objected to because of the following informalities:

Claims 8-10 encompass non-elected subject matter (See Reponse to Restriction Requirement, received 4 November 2003). Specifically, the elected invention is Group V, drawn to agents that counteract the influence of the mutant NPY gene by modulating its synthesis, secretion, or metabolism. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-10 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of Claims 8-10 encompasses methods of treating persons diagnosed as having an increased risk of developing a diabetic retinopathy due to the presence of mutation of leucine to proline at position 7 of the signal peptide of neuropeptide Y by administering any agent that counteracts the influence of the mutant neuopeptide Y gene. Claim 9 further limits this agent to any pharmaceutical that modulates any step in the synthesis, any step in the release, or any step in the metabolism of any endogenous neuropeptide Y gene, or any agent that modulates neuropeptide Y effects by interacting with any target receptor of neuropeptide Y. Claim 10 further limits the agent of Claim 8 to any pharmaceutical that modulates any step in the expression of any normal or mutant neuropeptide Y gene.

These agents of these claims are broad in scope, being defined on the basis of their effect, and not on any specific structure. The specification broadly discloses that such agents may encompass gene therapy to repair the mutant gene, pharmacotherapies that modulate the

synthesis, secretion or metabolism, as well as five receptors for neuropeptide Y, of which several drugs have been synthesized and found to interact with such receptors (p. 7). Moreover, antisense therapy is disclosed broadly, along with gene replacement and gene switching techniques (pp. 7-8).

In analyzing whether the written description requirement is met for gene claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, it appears that five drugs may have been synthesized that interact with neuropeptide Y receptors (p. 7) and a general description of mutant NPY alleles (p. 8). The specification does not provide any disclosure as to what would have been the required structure which would allow one to distinguish the various species of the genera. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e., other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other characteristics are the functional behaviors of the species of the genus.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds

of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of agents that counteract the influence of the mutant neuropeptide Y, whether by modulating synthesis, secretion, or metabolism or gene expression, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claims 8-10 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. These claims encompass methods of treating diabetic persons with an increased risk of developing diabetic retinopathy, due to the presence of a mutation of amino acid 7 of preproNPY from leucine to proline, by the administration of agents that counteract the influence of the mutant NPY gene. The claims are not enabled for any treatment, *in vivo*, or *ex vivo* by any agent that counteracts the mutant gene.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention, and that, therefore, Applicant's claims are not enabled.

The Breadth of the Claims

Claims 8-10 are broad in scope. Claim 8 encompasses methods for treating any diabetic person, diagnosed as having an increased risk of developing diabetic retinopathy on the basis of a mutation from leucine to proline at amino acid 7 of any preproNPY gene, by the administration of any agent that counteracts the influence of the mutant NPY gene and such administration may be through *in vivo* or *ex vivo* methods. Claim 9 limits the agent to any pharmaceutical that modulates any step in the synthesis, release, or metabolism of any endogenous NPY. Claim 10 limits the agent to any pharmaceutical that modulates any step in the gene expression, which encompasses any step in RNA transcription, protein translation, post-translational modification, protein trafficking, protein secretion, and protein degradation.

Because these claims are broad in scope, encompassing gene therapy and pharmaceutical treatment *in vivo* and *in vitro*, and such treatment effecting any steps manufacture, processing, metabolism and destruction of wild type or mutant NPY genes comprising a mutation causing

position 7 of preproNPY to be a proline, instead of the wild type leucine, in persons suffering from any type of diabetes, the detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide area of knowledge to a reasonably comprehensive extent. In other words, those aspects considered broad must be fleshed out to a reasonable extent so that one of ordinary skill in the art, at the time of invention by Applicant, would be able to practice the invention without an undue burden being imposed on such person of ordinary skill in the art (undue burden). However, as will be discussed below, Applicant has not met this burden.

The Nature of the Invention

The invention is in the nature of gene therapy or pharmaceutical therapy, *in vivo* or *ex vivo*, to reduce the risk of diabetic persons, whether type 1 or type 2 diabetes, developing diabetic retinopathy, which persons further comprise a mutation at position 7, from leucine to proline, in an NPY gene, comprising the administration by any method of any gene therapy composition or pharmaceutical that counteracts the influence of the mutant gene. Such compositions may do so by any method, including affecting the synthesis, release, metabolism, or degradation of the mutant, or any normal, NPY gene. Such gene therapy and pharmaceutical treatment is not in the field of predictable arts, and as such, is not enabling for most inventions in these arts.

With regard to gene therapy, while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be a difficulty as supported by numerous teachings available in the art. For example, Deonarain (1998) Expert Opin. Ther. Pat., 8: 53-69, indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at

adequeate levels for a long enough period of time" (p. 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (p. 65, CONCLUSION). Verma (1997) Nature, 389: 239-242, reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (p. 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery and this is the aspect we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression ... The use of viruses (viral vectors) is a powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses (e.g., p. 239, col. 3).

Further, Eck et al. (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, NY., pp. 77-101, states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the

cell, or its secretory fate, once produced, are all important factors for a successful gene therapy (e.g., bridging pp. 81-82). In addition, Gorecki (2001) Expert Opin. Emerging Drugs 6(2): 187-98) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g., ABSTRACT).

With regard to pharmaceuticals, similar arguments apply. To wit, one must account for the targeting of the effected tissues, entry into the cells of the tissues, localization of the pharmaceutical to the proper location within the cell, stability of the pharmaceutical throughout treatment, and degradation. Moreover, an accounting must be had that enough pharmaceutical reaches the target sites within the cells, has an effect, and has enough of an effect for a long enough period of time to effect treatment.

In reviewing the above-discussed problems, it is clear that the Artisan would therefore require, to make and/or use a new invention in the field, a showing that enough nucleic acid reaches the target cells (*in vivo*) or enough cells are transformed or effected (*ex vivo*), the gene therapy is incorporated, the gene therapy transcribes enough stable and functional mRNA, and proteins therefrom, or ribozymes, to effect treatment, or the pharmaceutical is present in high enough quantities to effect treatment. Alternatively, direct examples of such treatment would overcome this showing, because, if treatment is successful, it must have met the requirements.

The State of the Prior Art

The prior art with regard to such treatments for the development of diabetic retinopathy is sparse. Two recent articles demonstrate that NPY is associated with a wide spectrum of neurological activities, by Balasubramaniam (2003) Curr. Pharm. Design, 9:1165-75, and the association of the leu7 mutation to proline with high serum cholesterol by Karvonen, et al. (1998) Nature Med., 4(12): 1434-37. Lastly, Magni (2003) Curr. Protein and Peptide Science, 4: 45-57, provides a recent overview of the NPY system and the possibility of controlling NPY expression.

With regard to Balasubramaniam, a number of antagonists for NPY recepetors are discussed, and their influence on feeding and/or thermogenesis (ABSTRACT), but no mention is made with regard to retinopathy, or on the modulation of NPY synthesis, processing, or release. Therefore, Balasubramaniam provides no disclosure that would enable any aspect of Applicant's claims.

With regard to Karvonen, while the association of high serum cholesterol and LDL cholesterol levels with the subject mutation are made, no mention is made with regard to retinopathy, or on the modulation of NPY synthesis, processing, or release. Therefore, similar to Balasubramaniam, Karvonen provies no disclosure that would enable any aspect of Applicant's claims.

With regard to Magni, Magni demonstrates that NPY expression and function is part of a complex system controlling multiple functions, and its disruption may be relevant to disease states, such as obesity (ABSTRACT). Moreover, Magni shows that several agents can modulate

NPY and NPY-R expression (ABSTRACT). However, Magni has not shown any use of these agents in treating any diabetic retinopathy, or even provided anything beyond concept. Indeed, Magni states that "Future studies in this area might therefore result [in] possible therapeutic applications." (CONCLUSIONS). Here, Magni is specifically recognizing that the possible regulation of NPY expression may, in the future, yield useful treatments. Therefore, Magni recognizes that no current treatments, even as of 2003, are available for any disease, through the regulation of NPY expression.

Lastly, there is no art of record indicating that persons suffering from type 1 diabetes are even at an increased risk of diabetic retinopathy due to a mutation at position 7 of preproNPY from leucine to proline.

Hence, because the art is lacking enablement for novel gene therapy or pharmaceuticals for *in vivo* or *ex vivo* treatment of persons suffering from any diabetes and a mutation from leucine to proline at position 7 of a preproNPY gene for developing diabetic retinopathy, absent a largely enabling disclosure by Applicant, by way of specific direction, guidance, and examples, the invention claimed by applicant is not enabled whatsoever.

The Level of One of Ordinary Skill in the Art at the Time of Invention

The level of one of skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by

Applicant would not have been able to make and/or use the invention claimed without undue experimentation.

The Level of Predictability in the Art

Because the art, as shown above, does not disclose any therapeutic applications for reducing any risk of diabetic retinopathy *in vivo* or *ex vivo*, and very little in the way of successful gene therapy in general, the skilled artisan at the time of invention by Applicant could not predict, in the absence of proof to the contrary, that such applications would be efficacious in reducing the risk of developing diabetic retinopathy in any diabetic person.

Hence, absent a strong showing of guidance and direction and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

The Amount of Direction and Guidance Provided by Applicant

The Specification broadly discusses the correlation between Leu7/Pro mutations in preproNPY and various disease states (pp. 1-2), the treatment of such disease states with agents, including gene therapy (pp. 3-4), study results indicating the mutation increases the risk of type 2 diabetics developing retinopathy (p. 5), screening techniques (pp. 6-7), and various broadly discussed therapies (pp. 7-9). However, outside of these broad teachings and assertions, little in the way of specific direction or guidance is given as to how to administer such agents and effect such treatment of diabetic retinopathy *in vivo* or *ex vivo*, to any diabetic, regardless of type.

Because of the lack of specific direction and guidance that would allow one of skill in the art at the time of invention to reasonably predict that such treatments would be effective, the examples would be required to provide a very strong showing of effectiveness of such

treatments. Absent this strong showing, it would be have required undue experimentation to make and/or use the invention as claimed by Applicant.

The Existance of Working Examples

The Examples demonstrate a correlation between type 2 diabetics carrying a mutation in position 7 of preproNPY, from Leu to Pro, and the development of diabetic retinopathy, as well as various other vascular and cholesterol problems (pp. 10-15). Moreover, predicted secondary structures of preproNPY mRNAs are given (pp. 16-17), clinical characteristics of the study subjects (p. 18-19), and a covariance analysis of the mutation with carotid thickness (p. 20).

While applicant has shown an increased risk of developing diabetic retinopathy in type 2 diabetics, no increased risk is similarly shown in type 1 diabetics. Moreover, no treatment has been shown whatsoever in the examples of any sort.

The Quantity of Experimentation Needed to Make and/or Use the Invention

Because of the lack of working examples, insufficient guidance and direction provided by Applicant, the inherent unpredictability in the art, the state of the art, and the nature of the invention, even in the face of an advanced level of skill in the art, one of skill in the art would be required to perform a large amount of experimentation to make/and or use the invention as claimed by Applicant.

Conclusion

Because of the large amount of experimentation required to make and/or use the invention as claimed by Applicant, such experimentation is considered undue, and therefore, the claimed invention is not enabled for treating any diabetic person for development of diabetic

retinopathy, by the administration of any compound, whether *in vivo* or *ex vivo*, and whether such agent comprises gene therapy or pharmaceuticals aimed to modulate NPY expression.

CONCLUSION

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M Kelly whose telephone number is (703) 305-4460 and will be (571) 272-0729 after January 12, 2004. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051 and will be (571) 272-0734 after January 12, 2004. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1123.

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RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER